

A grayscale photograph of a doctor in a white lab coat sitting on a hospital bed, facing a patient who is also sitting on the bed. They appear to be in a conversation. The background shows a typical hospital room with medical equipment on the wall and a window with curtains.

Opioid Analgesia, Dependence, & Addiction **LINKED BY OPIOID REWARD**

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OXFORD

The Right to Pain Relief

And Other Deep Roots of the Opioid Epidemic

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Disclosures

- Board member, Physicians for Responsible Opioid Prescribing (unpaid)
- Based on an unpublished paper with Jane Ballantyne, Andrew Saxon
- Co-authored *The Right to Pain Relief and Other Deep Roots of the Opioid Epidemic* (Oxford, 2023) with Jane Ballantyne

Session Learning Objectives

- 01 | Review relationships among opioid analgesia, dependence, and addiction in DSM-IV and DSM-V.
- 02 | Identify and define the different forms of opioid dependence and their significance.
- 03 | Understand how opioid reward links opioid analgesia, opioid dependence, and opioid addiction.
- 04 | Understand that the traditional separation of chronic pain and addiction services may not be appropriate.



Case Study: Andrew

COPORATE DESIGNS

Meet Andrew

Age: 27; Occupation: Construction Worker

- Has worked in construction for five years after two years of community college
- Fell two years ago while carrying 2x4s, twisting his back, became unable to work
- Underwent L4-5 microdiscectomy a year and a half ago to remove herniated disc
- Temporary improvement in pain, brief return to work, then again unable to work
- Repeat MRI showed intact discs, no surgically correctable lesion
- Started oxycodone ER 20mg BID, allowed return to work
- After six months, needed dose increase to permit work, up to 40mg BID
- Now seeking additional dose increase to control pain, permit work
- Drinks beer 2-3 times per week, more on weekends, some cannabis



Opium and Opioids: Exogenous and Endogenous



Before the 1970s

Why does the sap from this flower relieve human pain better than any other substance?

Happy accident or gift from God?



After the 1970s

Exogenous opioid medications produce pain relief and other effects because they activate the specific opioid receptors of the endogenous opioid system (EOS).



In the 1980s

Stress-Induced Analgesia



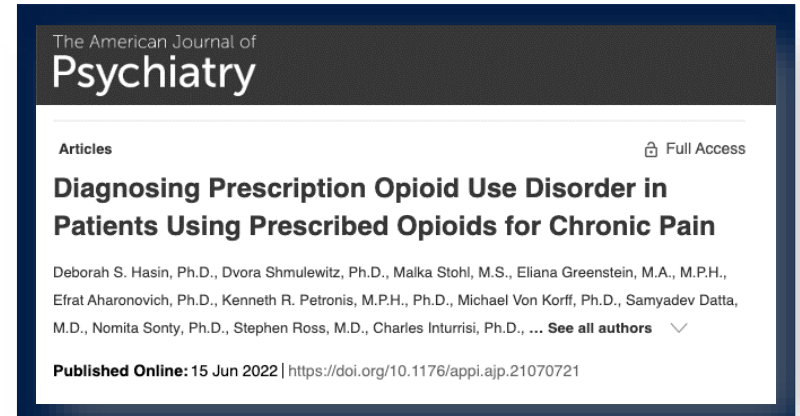
2024

The EOS continually regulates the balance between stress (not just pain) and reward to promote survival.

Opioids are not just targeted "painkillers" but general stress modulators (vs steroids).

Diagnosing Prescription Opioid Use Disorder in Patients Using Prescribed Opioids for Chronic Pain

Hasin et al. Am J Psychiatry, 2022



Study Design

Patients (N=5606) from pain clinics and inpatient substance treatment with a >30-day opioid prescription for chronic pain were evaluated for:

- **Unadjusted POUD**
- **DSM-5 opioid adjusted POUD**
i.e., withdrawal and tolerance excluded if patients used opioids only as prescribed
- **Pain-adjusted POUD**
behavioral criteria excluded if pain relief [therapeutic intent] was the sole motive

Results

Prevalence

of DSM-5 and pain-adjusted POUD

- 44% and 30% at the > 2-criteria threshold (mild)
- 29% and 25% at the > 4-criteria threshold (mod)

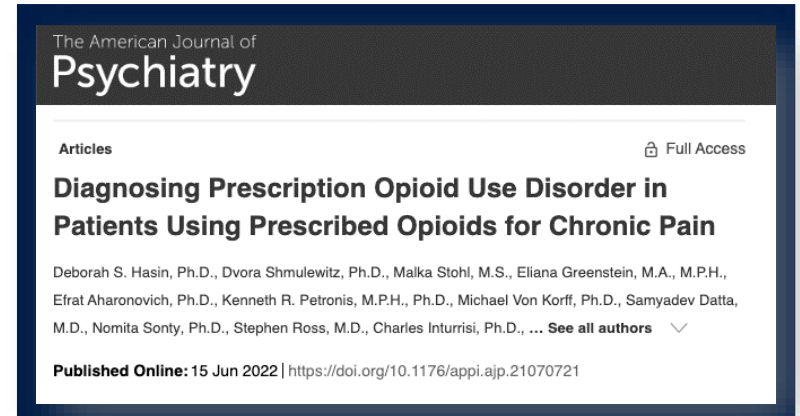
Pain adjustment

for therapeutic intent

- Little effect on prevalence among substance treatment patients
- But, substantially lowered prevalence among pain treatment patients

Diagnosing Prescription Opioid Use Disorder in Patients Using Prescribed Opioids for Chronic Pain, *Cont.*

Hasin et al. Am J Psychiatry, 2022



All 10 behavioral validators:

Had significantly stronger associations with pain-adjusted than with unadjusted or DSM-5 opioid-adjusted dimensional POUD measures (ratios of mean ratios, 1.22–2.31).

8 convergent validators:

Substance treatment, family history drug use disorders, other DSM-5 SUD, antisocial personality disorder, internalizing disorder (MDE, GAD, PTSD), tampering with medications, impulsivity, sensation seeking

2 divergent validators:

- worst pain past week
- prescription for legitimate reason

Hasin's Conclusions:

- 1 Adapting POUD measures for pain relief (therapeutic intent) improved validity (strength of relationship to validators) and lowered prevalence of POUD (mod) from 14% to 4%
- 2 Studies should investigate the clinical utility of differentiating between therapeutic and nontherapeutic intent in evaluating POUD diagnostic criteria

Opioid Adjustment of DSM-5 POUD Criteria: *Based on Outdated Science*

Exclusion of tolerance and withdrawal symptoms from DSM-V POUD criteria for those taking prescribed medications is based on the idea that these are expected and benign (Sullivan and Ballantyne 2022)

- *Not benign*: interdose opioid withdrawal symptoms are associated with POUD risk (Coloma-Carmona 2019)
- *Not “breakthrough pain”*: interdose opioid withdrawal can include pain (Rodriguez-Espinoza 2022)
- *Neither increases nor decreases in opioid dose have reliable effects on chronic pain severity (Krebs 2024)*
- But escalating opioid dose *is* associated with:
subsequent SUD – OUD – opioid OD – depression
& suicide (Hayes 2020, Martin 2011, Salas 2017,
Ilgen 2016, Degenhardt 2021)



Opioid Adjustment of DSM-5 POUD Criteria: *Based on Outdated Science* *Cont.*

- Tolerance and dependence are root causes of difficulty tapering LTOT in patients who are not benefitting and/or are at high risk for adverse outcomes.
- Therefore, these should be reinstated as part of the DSM-5 POUD criteria.



Pain-adjusted POUD Criteria: Therapeutic Intent Distinguishes Use vs. Abuse?

PAIN RELIEF

- Distinction between pain and mood targets is not consistent with current neurobiological and epidemiological research.
- Pain relief and mood elevation are both components of opioid reward.
 - Both pain and mood relief motivate prescription opioid use in patients with chronic pain (Carpenter 2019).
 - Relief of negative affect (hyperkatifeia) is proposed as a crucial intermediate step in the progression from impulsive to compulsive drug use (Koob 2020).
 - Depression is an important risk factor for long-term opioid use as well as opioid misuse, abuse, and OUD (Sullivan 2018).
 - Many chronic pain patients on long-term opioid therapy have significant psychiatric comorbidity, so opioid use is driven by both pain and mood relief.

Opioid Dependence – Fentanyl and Other Opioid Use Disorders: Treatment and Research Needs

Standard view that dependence arises after sustained exposure to opioids and is physical, temporary, and unrelated to addiction:

“Addiction should be differentiated from physical dependence, which occurs in most individuals even after a few opioid exposures and manifests with the emergence of withdrawal symptoms on opioid discontinuation.

Physical dependence resolves quickly and can be avoided by slowly tapering opioid medications. Improper management of physical dependence symptoms can result in persistent opioid use to overcome withdrawal that can eventually lead to addiction.”



“Opioids are initially used because of their rewarding effects or analgesic actions, but with repeated use, tolerance develops and higher doses are needed to produce the desired effects.”

SOURCE: Volkow, N. D., & Blanco, C. (2023). Fentanyl and Other Opioid Use Disorders: Treatment and Research Needs. The American journal of psychiatry, 180(6), 410–417.

Opioid Tolerance and Dependence

Three major types of tolerance:

PHARMACOKINETIC

PHARMACODYNAMIC

CONDITIONED

Cellular Desensitization

Opponent Processes

Opponent Processes:

- Drug effects are opposed by drug opposite effects to maintain homeostasis (incl. hedonic homeostasis) (Koob 2020, Ramsay 2014).
- Tolerance and withdrawal in compulsive drug use arise from counter-adaptive processes contributing to changes in motivation that drive opioid need and compulsive drug seeking.



Opioid Tolerance and Dependence

Biphasic response to opioid administration

“a-process” followed by “b-process”

Pharmacologically-induced
hedonically positive state

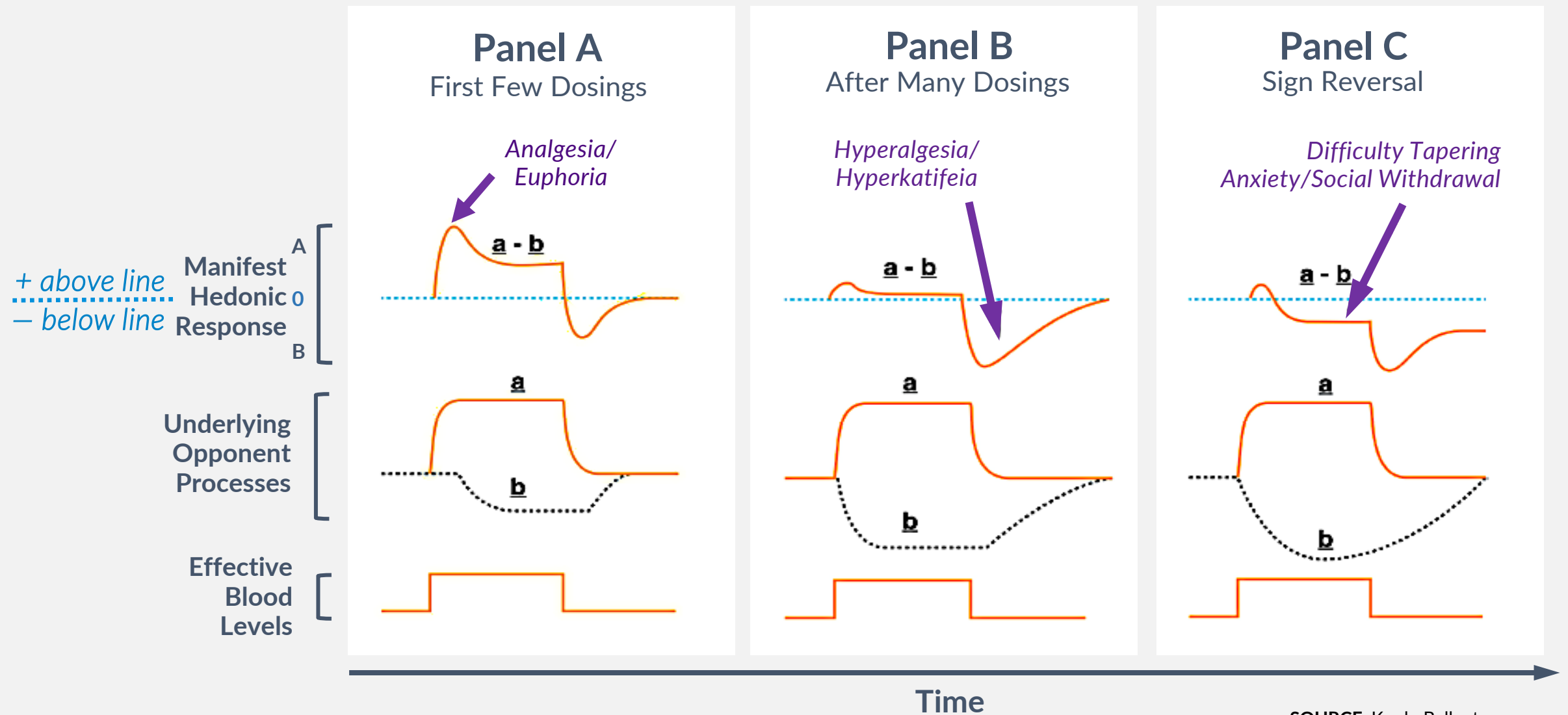
*initially
predominates*

A longer-lasting
hedonically negative state

*may persist long after
drug discontinuation
(e.g., *In Pain*, by
Travis Reider)*

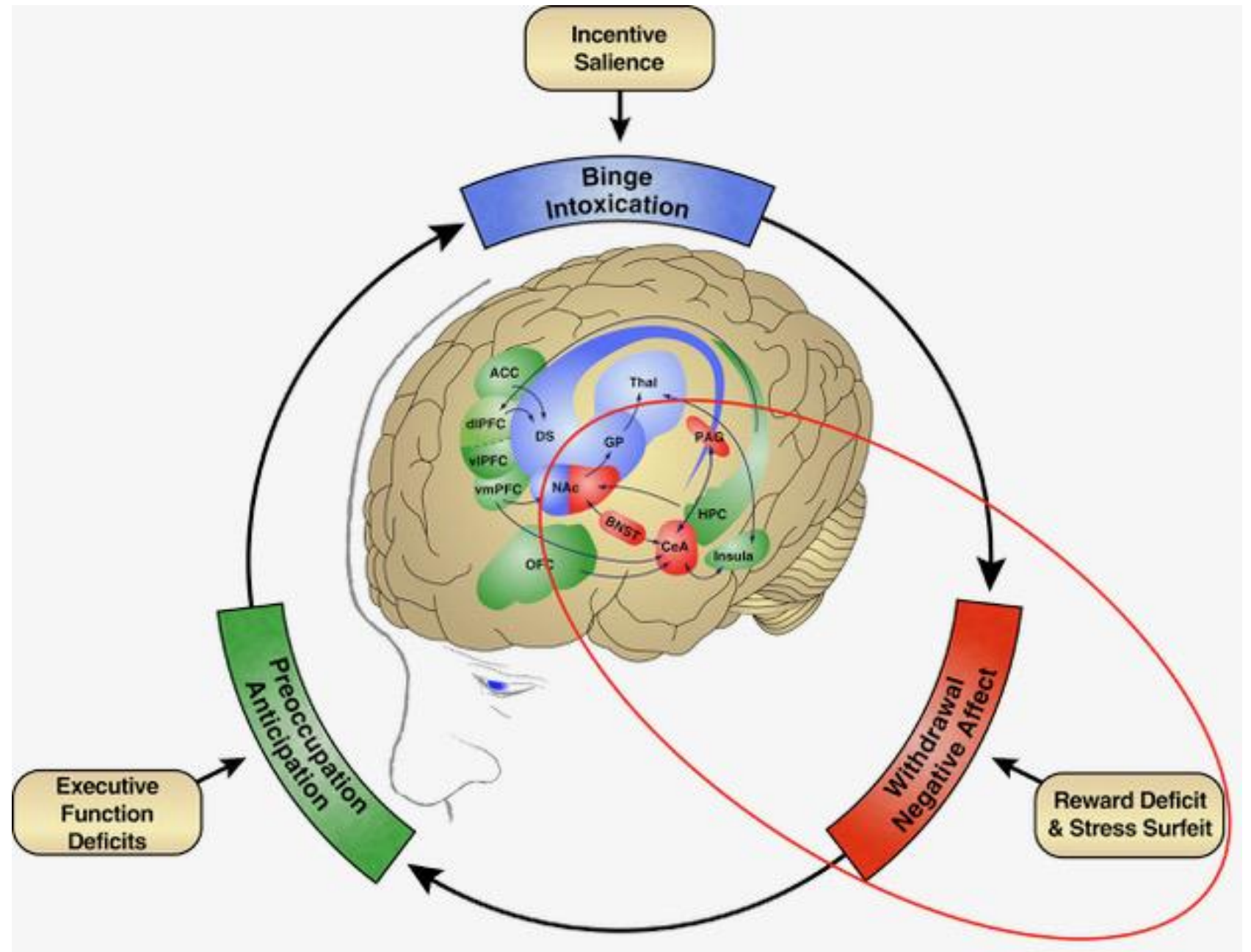



Role of Opioid Opponent Processes in Negative Reinforcement



Complex Persistent Opioid Dependence

similar to Koob's 'hyperkatefeia' second stage of addiction





Pain Affect and Opioid Misuse

- Exogenous opioid medications relieve pain affect or unpleasantness at lower doses than pain sensation or intensity. Patients on long-term opioid therapy use opioids to get relief from negative emotions (Gilam 2020).
- Mood disorders increase the risk of both chronic pain conditions and opioid misuse. These are associated with abnormalities of endogenous opioid function (Ballester 2022).
- This suggests that chronic pain, mood disorders, and opioid misuse can all be understood as disorders of reward processing (Elman and Borsook 2016).



Physical Pain and Opioid Misuse

Among US civilian prescription opioid users, the most common motive for opioid misuse (63%) is pain relief (Han 2017).

- Among these adult prescription opioid users, 12% reported misuse and of these, 17% reported POUD.
- Even among those with POUD, 49% reported pain as motivation for recent misuse.
- Opioid misuse solely for physical pain relief increased from 35% in young adults to 65% in older adults. In these older adults, 85% of all prescription opioid misuse episodes involved pain relief as a motive (Schepis 2020).
- This data suggests that we cannot simply rely on motivations for pain relief to distinguish opioid use from opioid misuse and abuse. (vs. Hasin)

Opioid Reward: Intrinsic and Extrinsic (*Pain Relief*)

Standard view: Opioid use for physical pain, opioid abuse for emotional pain.

- Parallel to opioid intrinsic reward vs. opioid extrinsic reward that arises from pain relief and is seen with other analgesics that are not intrinsically rewarding (e.g., acetaminophen). But the relationship between these shifts over time and appears to be context dependent (Navratilova 2015, 2016).
- Repeated opioid use shifts the reward/anti-reward balance so that natural non-drug rewards lessen while anti-reward increases, motivating opioid use to compensate for these (Koob 2014) .



Opioid Reward: Intrinsic and Extrinsic (*Pain Relief*)

Borsook et al. (2016)

argue that a reward deficit state can be caused by chronic pain and/or repeated opioid use, resulting in a loss of positive affect or anhedonia.

Review

> *Neurosci Biobehav Rev.* 2016 Sep;68:282-297.
doi: 10.1016/j.neubiorev.2016.05.033. Epub 2016 May 28.

Reward deficiency and anti-reward in pain chronification

D Borsook ¹, C Linnman ², V Faria ³, A M Strassman ⁴,
L Becerra ⁵, I Elman ⁶

Finan et al. (2018)

argue that chronic pain is often characterized by deficits in positive affect and that these are associated with opioid misuse.

Review

> *Prog Neuropsychopharmacol Biol Psychiatry.*
2018 Dec 20;87(Pt B):255-262.
doi: 10.1016/j.pnpbp.2017.07.029. Epub 2017 Aug 1.

The risk for problematic opioid use in chronic pain: What can we learn from studies of pain and reward?

Patrick H Finan ¹, Bethany Remeniuk ², Kelly E Dunn ²

Garland et al. (2023)

have shown that enhancing sensitivity to natural, non-drug rewards can remediate the anhedonia associated with chronic opioid use.

Randomized Controlled Trial

> *Psychol Med.* 2023 Apr;53(5):2085-2094.
doi: 10.1017/S0033291721003834. Epub 2021 Oct 14.

Mindfulness-Oriented Recovery Enhancement remediates anhedonia in chronic opioid use by enhancing neurophysiological responses during savoring of natural rewards

Eric L Garland ^{1 2 3}, Spencer T Fix ⁴, Justin P Hudak ^{1 2},
Edward M Bernat ⁴, Yoshio Nakamura ^{1 5}, Adam W Hanley ^{1 2},
Gary W Donaldson ⁵, William R Marchand ^{3 6}, Brett Froeliger ⁷

These suggest that non-drug reward and mood are essential to understanding opioid misuse.



Opioid Analgesia, Dependence, Addiction: Summary So Far

- The evidence that sustained opioid exposure (for analgesia) leads to opioid dependence is **quite strong**.
- The evidence that this dependence can be long-lasting and include symptoms of reward deficiency (anhedonia) and anti-reward (anxiety, insomnia) is **suggestive**, but we do not have official diagnostic criteria or prevalence rates for this complex form of opioid dependence (PODS, Edmond, 2023).
- The evidence that opioid dependence is an important pre-addictive state that significantly increases the risk of progression to addiction is **quite preliminary**.

From Opioid Dependence to Opioid Addiction

- In opioid dependence, opioid reward is no longer an episodic phenomenon as opioid need has become continuous.
- Opioid reward now involves not only pain relief, but the relief of the ongoing reward deficiency (anhedonia) and anti-reward (anxiety, irritability, insomnia) states.
- As opioid dependence progresses toward opioid addiction, opioid reward becomes not only pervasive, but more important than most or all other natural rewards.



From Opioid Dependence to Opioid Addiction: role of craving

One indicator of this progression is opioid craving.

- Research on craving that used single item scales found a relationship among opioid craving, negative affect and opioid misuse, but often found little relationship between opioid craving and pain (Martel 2014).
- Research using multidimensional measures of craving has found that the desire-and-intention to use prescription opioids and craving for relief from negative states were significantly associated with having experienced pain over the past three months, pain severity, number of pain locations, and pain interference. (Ashrafioun 2016).





From Opioid Dependence to Opioid Addiction

- Garland's model of chronic pain and opioid addiction asserts that individuals crave opioids to maintain psychological well-being when experiencing recurrent pain. Individuals use opioids to relieve pain-related stress and to relieve negative emotions (Garland, 2013).
- Attentional bias favoring opioids and cue-elicited craving predicted opioid misuse risk 20 weeks later after controlling for pre-treatment opioid dependence diagnosis, opioid misuse, and pain severity (Garland, 2014).
- Psychological distress and catastrophizing predicted cue-elicited opioid craving, whereas pain severity did not. Higher levels of distress predicted craving only among misusing group (Parisi, 2022).

Conclusion:

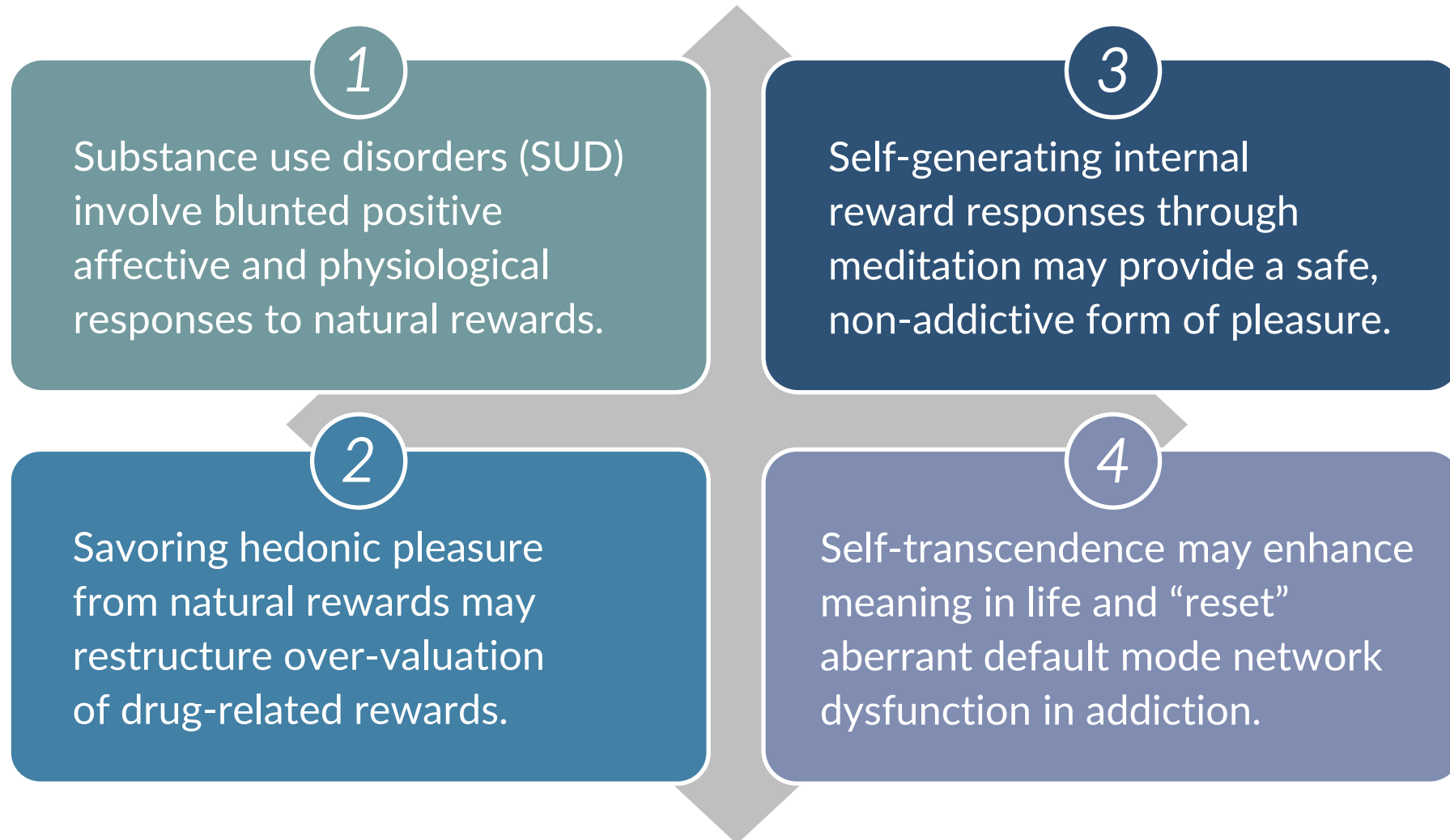
Although opioids are prescribed for analgesia, negative cognitive-emotional reactivity, both in general and specific to pain, enhances cue-elicited opioid craving beyond pain severity alone.

Shifting opioid reward as opioid recipients progress from opioid analgesia to dependence to addiction

A proposed framework:

- With opioid analgesia, opioid reward is episodic
- Once opioid dependence occurs, opioid reward has become pervasive
- When opioid addiction develops, opioid reward has become dominant

Garland's Restructuring Reward Hypothesis





How should we understand opioid risk in patients on LTOT for chronic pain?

- A patient's stated reasons for taking opioids may not be as important as the dose and duration of opioid exposure in determining opioid risk (like corticosteroids, Clauw 2017).
- Opioid misuse and POUD risks do not only arise from patient misbehavior or improper intentions. They are intrinsic to opioids and the roles they play in the human brain.
- Similar lesson: The first CDC studies of opioid OD in WV pointed to doctor-shopping and med diversion as causes of OD. (Hall 2008) But later studies showed risk was related to the prescribed dose of opioids – intrinsic risk (Dunn 2010).



How should we understand opioid risk in patients on LTOT for chronic pain?

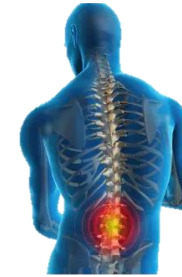
Now we must learn a similar lesson about opioid misuse.

- Endogenous opioids modulate both physical pain and social pain to promote human survival (Ballantyne and Sullivan 2017).
- It is not possible for laws or diagnostic criteria to pull these apart into entirely separate categories of legitimate opioid use for pain relief and illegitimate opioid misuse for mood relief.



Does Andrew have POUD?

Age: 27; Occupation: Construction Worker



- States that he takes his oxycodone for "breakthrough pain" relief. He needs more because the old doses no longer provide the relief he needs. The relief provided by his original dose of oxycodone no longer lasted long enough for him to get through his workday.
- He does like the "mental break" that oxycodone provides him, especially when he drinks a beer or two with it.
- Andrew's initial dose was 20mg BID (60 MED), then it was increased to 40mg BID (120mg MED). He has been taking extra doses as needed. He is asking for further increase.
- Andrew sees his functional impairments as due to his pain, and his opioids as reducing these impairments.
- He needs treatment that integrates both pain and addiction services.



Pain and Suffering: Medical and Non-Medical

- During the past 200 years, we have **separated pain from the rest of human suffering** as a uniquely mechanical and passive affliction, giving it wholly to medicine to predict, explain, and control.
- Since the 1914 Harrison Narcotic Act, **legitimate opioid use** has been restricted to prescribed opioids for the treatment of physical pain. Any opioid use for the treatment of social or psychological pain is considered **opioid abuse**.
- These have been combined into a patient's **right to pain relief** through prescribed opioids.

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The Right to Pain Relief

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Chapter Titles

Preface

Chapter 1. The Problems of Pain in Western Society

Chapter 2. The Medical Dream of Conquering Pain

Chapter 3. The Emergence of a Right to Pain Relief

Chapter 4. Chronic Pain as a Disease

Chapter 5. Looking Beyond a Biopsychosocial Model of Pain

Chapter 6. Pain Medicine and the Medicalization of Chronic Pain

Chapter 7. Selling Opioids as Targeted Painkillers

Chapter 8. From Causal to Moral Models of Pain and the Right to Pain Relief

Chapter 9. Finding a Place for Pain in Medicine, in Policy, and in Life

Clinician Epilogue

Patient Epilogue

Knowledge Check

Which of the following about opioid dependence is true?

A

Opioid dependence resolves quickly and can be avoided by slowly tapering opioid medications.

B

Endogenous opioids function as the brain's own painkillers.

C

Pharmacodynamic opioid tolerance can be explained as a process of cellular desensitization.

D

Until the 1914 Harrison Narcotic Act, opioids were freely available without prescription.

Knowledge Check

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